PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4 -32611A/USN	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/08720	International filing date *(day/month/year)* 06.08.2003	Priority date *(day/month/year)* 07.08.2002
International Patent Classification (IPC) or both national classification and IPC C07D487/04		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 13 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.01.2004	15.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Goss, I Telephone No. +49 89 2399-8292

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/08720

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-87 as originally filed

Claims, Numbers

1-27 received on 11.08.2004 with letter of 10.08.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/08720

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 12-18

   because:

   ☒ the said international application, or the said claims Nos. 12-18 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11,19-27
	No:	Claims	12-18

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 12 to 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty

The subject-matter claimed refers to bicyclic imidazole and triazole derivatives of formula I, pharmaceutical composition containing them, methods for preparing said compounds.

Claim 1 according to the set of claims as filed on 10.08.2004, includes disclaimers which indeed exclude all the compounds disclosed in D1 to D4 which are considered accidental disclosures. The present wording of independent claims 1, 19 (and dependent claim 20) as well as 26 is acceptable.

Novelty can be recognized.

Inventive step

The problem underlying the present application appears to reside in the provision of compounds which are inhibitors of the 450 enzyme, aldosterone synthase and thus may be useful in the treatment of aldosterone mediated pathological conditions.

The solution to the stated problem resides in the provision of compounds of general formula I being bicyclic imidazole and triazole derivatives characterized by the presence of a substituent (R_2) at position 7 or 8.

Data are given on pages 29 to 32 in terms of in vitro aldosterone synthase and aromatase inhibitory activity as well as in vivo activity for reduction of cardiac damage.

The only prior art describing compounds useful in the treatment and prevention of i.a. prostatic cancer, prostatic hypertrophy or mammary cancer is represented by D4. No data are given with respect to the specific pharmacological profile of the compounds as presently claimed. From the prior art the skilled person would have not taken the incentive to provide the present compounds expecting them to act in this specific technical field.

In the absence of any relevant prior art, the significant difference illustrates the non obviousness of the claimed compounds, and can thus , indeed form an argument in support of the presence of an inventive step. Although the examiner is now prepared, in principle, to recognize an inventive step mainly in view of the fact that the core novel structure (only slightly differently substituted) has been clearly demonstrated to be indeed active (see tested compounds 1,3 and 32), the applicant is reminded that

a) in order to demonstrate an inventive step the patent application has to solve a technical problem and thereby make a technical contribution to the art. The problem to be solved should be solved by the whole scope of the claimed subject-matter and not just by individual compounds tested. If this were not the case an invention could arbitrarily be broadened to any limit without consideration whether the compounds are actually solving the problem underlying the invention.

An inventive step could be in principle recognized (the aspect of the breadth will be eventually considered in the next phase).

Industrial applicability

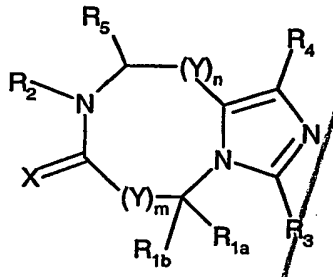
For the assessment of the present claims 12 to 18 the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Further points

The expression "lower" used in the claims (namely for alkyl in claims 4 to 7,) is considered to be unclear in scope, since it does not precisely define the matter for which protection is sought, especially the upper limit . Therefore the terms including the prefix "lower" should be specified according to the disclosure in the description.

What is claimed is:

1. A compound of formula I



(I)

wherein

X is oxygen or H_2;

Y is -CRR'- in which

R and R' are independently hydrogen, optionally substituted alkyl, aralkyl or heteroaralkyl;

R_{1a} is hydrogen, optionally substituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heterocyclyl or heteroaralkyl provided that R_{1a} is not 9H-carbazol-2-yl when R_2 is methyl, m is zero or an integer of 1, n is zero, X is H_2, and R_{1b}, R_3, R_4 and R_5 are hydrogen;

R_{1b} is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

R_2 is R_6-$(CHR_7)_p$- in which

R_6 is optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl;

R_7 is hydrogen, optionally substituted alkyl, aryl, heteroaryl or aralkyl;

p is zero or an integer from 1 to 4;

R_3 and R_4 are independently hydrogen, halogen, optionally substituted alkyl, aryl or heteroaryl; or

R_4-C may be replaced by nitrogen;

R_5 is hydrogen, optionally substituted alkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

m and n are independently zero or an integer of 1 provided that the sum of m and n is not 2;

or a pharmaceutically acceptable salt thereof; or a diastereomer thereof; or a mixture of diastereomers thereof; or an optical isomer thereof; or a mixture of optical isomers thereof.

2. A compound according to claim 1 wherein

Y is -CRR'- in which R and R' are hydrogen;

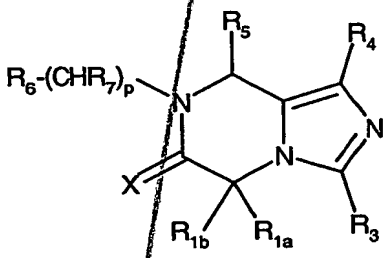
or a pharmaceutically acceptable salt thereof; or a diastereomer thereof; or a mixture of diastereomers thereof; or an optical isomer thereof; or a mixture of optical isomers thereof.

3. A compound according to claim 2 wherein

m and n are zero;

or a pharmaceutically acceptable salt thereof; or a diastereomer thereof; or a mixture of diastereomers thereof; or an optical isomer thereof; or a mixture of optical isomers thereof.

4. A compound according to claim 3 of formula IA



(IA)

wherein

X is oxygen or H_2;

R_{1a} is lower alkyl, aryl or heteroaryl provided that R_{1a} is not 9H-carbazol-2-yl when R_6 is methyl, p is zero, X is H_2, and R_{1b}, R_3, R_4 and R_5 are hydrogen;

R_{1b} is hydrogen, lower alkyl, aralkyl or heteroaralkyl;

R_6 is cycloalkyl, aryl or heteroaryl;

R_7 is hydrogen or lower alkyl;

p is zero or an integer of 1 or 2;

R_3, R_4 and R_5 are hydrogen;

or a pharmaceutically acceptable salt thereof; or a diastereomer thereof; or a mixture of diastereomers thereof; or an optical isomer thereof; or a mixture of optical isomers thereof.

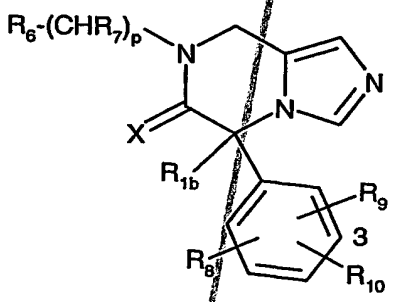
5. A compound according to claim 4 wherein

R_{1a} is monocyclic aryl;

R_{1b} is hydrogen, lower alkyl or aralkyl;

or a pharmaceutically acceptable salt thereof; or a diastereomer thereof; or a mixture of diastereomers thereof; or an optical isomer thereof; or a mixture of optical isomers thereof.

6. A compound according to claim 5 of formula IB



(IB)

wherein

X is oxygen or H_2;

R_{1b} is hydrogen, lower alkyl or aralkyl;

R_6 is cycloalkyl, aryl or heteroaryl;

R_7 is hydrogen or lower alkyl;

p is zero or an integer of 1 or 2;

R_8, R_9 and R_{10} are independently hydrogen, hydroxy, halogen, cyano, nitro, trifluoromethyl, optionally substituted alkyl, cycloalkyl, optionally substituted amino, alkoxy, alkylthio, carboxy, sulfonyl, carbamoyl, aryl, aryloxy, arylthio or heterocyclyl;

or a pharmaceutically acceptable salt thereof; or a diastereomer thereof; or a mixture of diastereomers thereof; or an optical isomer thereof; or a mixture of optical isomers thereof.

7. A compound according to claim 6 of wherein

X is oxygen or H_2;

R_{1b} is hydrogen, lower alkyl or aralkyl;

R_6 is cycloalkyl, aryl or heteroaryl;

R_7 is hydrogen or lower alkyl;

p is an integer of 1;

R_8 is hydrogen;

R_9 is hydrogen, halogen, cyano or trifluoromethyl;

R_{10} is halogen, cyano or trifluoromethyl;

or a pharmaceutically acceptable salt thereof; or a diastereomer thereof; or a mixture of diastereomers thereof; or an optical isomer thereof; or a mixture of optical isomers thereof.

8. A compound according to claim 7 wherein

X is oxygen;

or a pharmaceutically acceptable salt thereof; or a diastereomer thereof; or a mixture of diastereomers thereof; or an optical isomer thereof; or a mixture of optical isomers thereof.

9. A compound according to claim 7 wherein

R_6 is C_{3-6}cycloalkyl, monocyclic aryl or monocyclic heteroaryl;

or a pharmaceutically acceptable salt thereof; or a diastereomer thereof; or a mixture of diastereomers thereof; or an optical isomer thereof; or a mixture of optical isomers thereof.

10. A compound according to claim 7 wherein

R_{10} is located at the 3-position;

or a pharmaceutically acceptable salt thereof; or a diastereomer thereof; or a mixture of diastereomers thereof; or an optical isomer thereof; or a mixture of optical isomers thereof.

11. A compound according to claim 1 which is selected from:

4-(7-Cyclopropylmethyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

4-(7-Methyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

4-(7-Benzyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

4-(7-Allyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

4-(6-Oxo-7-propyl-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

4-(7-Isopropyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

4-{7-[2-(4-Fluoro-phenyl)-ethyl]-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl}-benzonitrile;

4-[7-(3-Morpholin-4-yl-propyl)-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl]-benzonitrile;

7-(4-Methoxy-benzyl)-5-(4-thiophen-3-yl-phenyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

4-[7-(4-Methyl-benzyl)-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

4-[7-(4-Chloro-benzyl)-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl]-benzonitrile;

4-[6-Oxo-7-(4-trifluoromethyl-benzyl)- 5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzo nitrile;

4-[6-Oxo-7-(3-methyl-benzyl)- 5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

4-[6-Oxo-7-(4-fluoro-benzyl)- 5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

4-[6-Oxo-7-(3-trifluoromethyl-benzyl)- 5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

4-[6-Oxo-7-(3, 4-dichloro-benzyl)- 5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

4-(7-Cyclopropyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

4-(7-Cyclohexyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

4-(7-Cyclopentyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

4-[7-(2-Methoxyethyl)-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl]-benzonitrile;

4-[7-(3-Methoxypropyl)-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl]-benzonitrile;

4-(6-Oxo-7-pyridin-4-ylmethyl-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

7-Benzyl-5-phenyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

7-Methyl-5-phenyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(4-Bromo-phenyl)-7-methyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(4-Bromo-phenyl)-7-(4-methoxy-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(4-Bromo-phenyl)-7-cyclopropylmethyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

7-Benzyl-5-(4-bromo-phenyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(4-Bromo-phenyl)-7-(4-chloro-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(4-Bromo-phenyl)-7-(4-trifluoromethyl-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(4-Bromo-phenyl)-7-(4-methoxy-phenyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(4-Bromo-phenyl)-7-(4-fluoro-phenethyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(4-Bromo-phenyl)-7-(4-fluoro-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-methyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-cyclohexyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-(4-methoxy-phenyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-cyclopropylmethyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

7-Benzyl-5-(3-bromo-phenyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-(4-methoxy-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-(4-fluoro-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-(4-chloro-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-(4-methyl-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-(4-trifluoromethyl-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-(3-trifluoromethyl-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-(3-fluoro-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-(3-methyl-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-(phenethyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-(4-methoxy-phenethyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-(4-chloro-phenethyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-(3-chloro-phenethyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-(4-methyl-phenethyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-(4-fluoro-phenethyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-thiophen-2-ylmethyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-furan-2-ylmethyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-thiophen-3-ylmethyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-furan-3-ylmethyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-pyridin-3-ylmethyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-pyridin-2-ylmethyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-pyridin-4-ylmethyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-cyclohexylmethyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

4-[5-(3-Bromo-phenyl)-6-oxo-5,6-dihydro-8H-imidazo[1,5-a]pyrazin-7-ylmethyl]-piperidine-1-carboxylic acid *t*-butyl ester;

5-(3-Bromo-phenyl)-7-piperidin-4-ylmethyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

(*R*)-5-(3-Bromo-phenyl)-7-((*R*)-1-phenyl-ethyl)-7, 8-dihydro-imidazo[1,5-a]pyrazin-6-one;

(*S*)-5-(3-Bromo-phenyl)-7-((*R*)-1-phenyl-ethyl)-7, 8-dihydro-imidazo[1,5-a]pyrazin-6-one;

(*R*)-5-(3-Bromo-phenyl)-7-((*S*)-1-phenyl-ethyl)-7, 8-dihydro-imidazo[1,5-a]pyrazin-6-one;

(*S*)-5-(3-Bromo-phenyl)-7-((*S*)-1-phenyl-ethyl)-7, 8-dihydro-imidazo[1,5-a]pyrazin-6-one;

(*R*)-5-(4-Bromo-phenyl)-7-((*R*)-1-phenyl-ethyl)-7, 8-dihydro-imidazo[1,5-a]pyrazin-6-one;

(*S*)-5-(4-Bromo-phenyl)-7-((*R*)-1-phenyl-ethyl)-7, 8-dihydro-imidazo[1,5-a]pyrazin-6-one;

(*R*)-5-(4-Bromo-phenyl)-7-((*S*)-1-phenyl-ethyl)-7, 8-dihydro-imidazo[1,5-a]pyrazin-6-one;

(*S*)-5-(4-Bromo-phenyl)-7-((*S*)-1-phenyl-ethyl)-7, 8-dihydro-imidazo[1,5-a]pyrazin-6-one;

4-[(*R*)-6-Oxo-7-((*S*)-1-phenyl-ethyl)-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl]-benzonitrile;

4-[(*S*)-6-Oxo-7-((*S*)-1-phenyl-ethyl)-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl]-benzonitrile;

7-Benzyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

7-(4-Methyl-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

7-(4-Fluoro-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

3-(7-Benzyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

3-[7-(4-Methyl-benzyl)-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl]-benzonitrile;

3-[7-(4-Fluoro-benzyl)-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl]-benzonitrile;

3-[7-(4-Chloro-benzyl)-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl]-benzonitrile;

3-[7-(4-Methoxy-benzyl)-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl]-benzonitrile;

3-[7-(4-Fluoro-phenethyl)-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl]-benzonitrile;

3-(7-Phenethyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

3-(7-Cyclopropylmethyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

5-(4'-Chloro-biphenyl-4-yl)-7-(4-methoxy-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

7-(4-Methoxy-benzyl)-5-(4-thiophen3-yl-phenyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

7-Cyclopropylmethyl-5-(4-thiophen-3-yl-phenyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

7-Benzyl-5-(4'-fluoro-biphenyl-3-yl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-Biphenyl-4-yl-7-(4-fluoro-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

7-Benzyl-5-biphenyl-3-yl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

Methyl 4-(7-benzyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzoate;

4-(7-Benzyl-5-methyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

5-(4-Bromo-phenyl)-7-cyclopropylmethyl-5-methyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(3-Bromo-phenyl)-7-cyclopropylmethyl-5-methyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

5-(4-Bromo-phenyl)-7-(4-fluoro-benzyl)-5-methyl-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

4-[7-(4-Fluoro-benzyl)-5-methyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl]-benzonitrile;

4-{(*R*)-7-[(*S*)-1-(4-Fluoro-phenyl)-ethyl]-5-methyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl}-benzonitrile;

4-{(*S*)-7-[(*S*)-1-(4-Fluoro-phenyl)-ethyl]-5-methyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl}-benzonitrile;

5-Benzyl-5-(4-bromo-phenyl)-7-(4-fluoro-benzyl)-7,8-dihydro-imidazo[1,5-a]pyrazin-6-one;

4-(5,7-Dibenzyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

4-(5-Benzyl-7-cyclopropylmethyl-6-oxo-5,6,7,8-tetrahydro-imidazo[1,5-a]pyrazin-5-yl)-benzonitrile;

5-(4-Bromophenyl)-7-(4-methoxy-benzyl)-5,6,7,8-tetrahydro-imidazo[1,5-a]-pyrazine;

4-(8-Benzyl-7-oxo-6,7,8,9-tetrahydro-5H-imidazo[1,5-a][1,4]diazepin-5-yl)-benzonitrile; and

4-(8-Cyclopropylmethyl-7-oxo-6,7,8,9-tetrahydro-5H-imidazo[1,5-a][1,4]diazepin-5-yl)-benzonitrile;

or a pharmaceutically acceptable salt thereof; or an optical isomer thereof; or a mixture of optical isomers thereof.

12. A method for the inhibition of aldosterone synthase activity in mammals which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

13. A method for the prevention and/or treatment of conditions associated with aldosterone synthase activity in mammals which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

14. The method according to claim 13, which method comprises administering said compound in combination with a therapeutically effective amount of anti-obesity agent, anti-hypertensive agent, inotropic agent or hypolipidemic agent.

15. A method for the treatment of hypokalemia, hypertension, congestive heart failure, atherosclerosis, coronary heart diseases and post myocardial infarction, which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

16. A method for the treatment of restenosis, increased formation of collagen, fibrosis, and remodeling following hypertension and endothelial dysfunction, which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

17. A method for the treatment of renal failure and nephropathy, which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

18. A method for the treatment of syndrome X and obesity, which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

19. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with one or more pharmaceutically acceptable carriers.

20. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with a therapeutically effective amount of anti-obesity agent, anti-hypertensive agent, inotropic agent or hypolipidemic agent.

21. A pharmaceutical composition according to claim 19 or 20 for the treatment of hypokalemia, hypertension, congestive heart failure, atherosclerosis, coronary heart diseases, post myocardial infarction, restenosis, increased formation of collagen, fibrosis, remodeling following hypertension and endothelial dysfunction, renal failure, nephropathy, syndrome X and obesity.

22. A compound of formula 1 according to claim 1, for use as a medicament.

23. Use of a compound of formula 1 according to claim 1, for the preparation of a pharmaceutical composition for the treatment of conditions associated with aldosterone synthase activity.

24. A pharmaceutical composition according to claim 19 or 20, for use as medicament.

25. Use of a pharmaceutical composition according to claim 19 or 20, for the preparation of a medicament for the treatment of conditions associated with aldosterone synthase activity.

26. Use according to any one of claims 23 or 25 wherein the conditions associated with aldosterone synthase activity is selected from hypokalemia, hypertension, congestive heart failure, atherosclerosis, coronary heart diseases, post myocardial infarction, restenosis, increased formation of collagen, fibrosis, remodeling following hypertension and endothelial dysfunction, renal failure, nephropathy, syndrome X and obesity.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 03/08720

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/519 A61K31/5517 A61P5/40
//(C07D487/04,241:00,235:00),(C07D487/04,243:00,235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YAMAUCHI, MASAHIGE ET AL: "Reactivity of 2,4(5)-dialkylimidazoles. Synthesis of 6,7,8,9-tetrahydro-5H-imidazo'1,5-a!'1,4!diazepine derivatives" CHEMICAL & PHARMACEUTICAL BULLETIN (1976), 24(7), 1480-4 , XP009019004 page 1481, compounds of general formula IV ---	1
X	YAMAUCHI, MASASHIGE ET AL: "Synthesis of 6,7,8,9-tetrahydro-5H-imidazo'1,5-a!'1,4!diazepines" CHEMISTRY & INDUSTRY (LONDON, UNITED KINGDOM) (1976), (1), 31-2 , XP009019005 page 32, compounds of genearl formula IV --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 October 2003	07/11/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goss, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

[redacted]

Internat[redacted]l Application No
P[redacted]P 03/08720

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	JANIN Y L ET AL: "Imidazo'1,5-g!'1,4!diazepines, TIBO Analogues Lacking the Phenyl Ring: Synthesis and Evaluation as Anti-HIV Agents" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 52, no. 48, 25 November 1996 (1996-11-25), pages 15157-15170, XP004105102 ISSN: 0040-4020 page 15159; examples 13A,B	1
X	WO 97 00257 A (YAMANOUCHI PHARMA CO LTD ;YODEN TORU (JP); OKADA MINORU (JP); ISHI) 3 January 1997 (1997-01-03) examples 9,12A,18A,22A	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/08720

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9700257 A	03-01-1997	AU 6015796 A	15-01-1997
		WO 9700257 A1	03-01-1997